CHANNEL, 1998c

DEPARTMENT OF THE AIR FORCE
AIR FORCE RESEARCH LABORATORY (AFMC)
WRIGHT-PATTERSON AIR FORCE BASE OHIO 45433

18 Dec 1998

MEMORANDUM FOR EPA
NCEA (MD-52)
RTP, NC 27711
ATTN: Annie Jarabek

FROM: AFRL/HEST
2856 G Street, Bldg 79
Wright-Patterson AFB OH 45344-7400

SUBJECT: Consultative Letter; AFRL-HE-WP-CL-1998-0031, Pharmacokinetic Study of Perchlorate Administered Orally to Humans

1. The Operational Toxicology Branch intends to collaborate on a 14-day dosing study for perchlorate with human subjects to be conducted by Dr Georg Brabant at the Medizinische Hochschule in Hannover, Germany. The study has been approved by the Ethical Committee at the Medizinische Hochschule and will start as early as January 1999. An outline of the study is Attachment 1. The translated text of the submission to the Ethical Committee is Attachment 2. The intent of the study is to compare data from human endpoints with data from rat studies, especially rat iodine and perchlorate kinetic studies. A single dose study with perchlorate and radiolabeled iodide in humans is also under consideration pending approvals and funding.

2. The technical point of contact for this collaboration is David R. Mattie, PHD. He can be reached at the above address or by phone at 937-255-3423, extension 3105.

STEPHEN R. CHANNEL, Maj, USAF, BSC
Chief, Operational Toxicology Branch
Human Effectiveness Directorate

Attachment 1. OUTLINE OF 14 -DAY HUMAN PERCHLORATE STUDY

Number of doses: 3 (1.0, 0.1 mg/kg/day plus one dose higher or lower depending on results of animal studies); Dissolve in glass of water and drink all at once.

No control group: Each individual would serve as their own control - 2 week placebo followed by 2 weeks of perchlorate, followed by minimum 5 day recovery.

Number of Subjects: 7/ dose; same sex, body weight, age and %body fat; will use narrow range for BW, age and body fat.

Parameters to be measured:

- Cytopuncture of the thyroid would be performed at the end of the perchlorate exposure using a fine needle to biopsy thymocytes for PCR determination and iodide concentration. By Medizinische Hochschule

- Ultrasound of the thyroid would be performed weekly. By Medizinische Hochschule

- Blood would be drawn by Medizinische Hochschule weekly for:
    - TSH, T4, T3 and Tg measurement by Medizinische Hochschule
    - CBC by Medizinische Hochschule
    - iodine by the Univ of Wuerzburg or AFRL/HEST

- Blood would be drawn by Medizinische Hochschule for:
    - perchlorate in serum by HEST. See below.

- Body weight by Medizinische Hochschule

- Urine collection: total 24 hour urine on the first day and after days 7 (from first dose on day 7 up to first dose on day 8) and 14 (starting after last dose of the study) and after days 1-3 of recovery (on day 1,2,3 of recovery collect first void of the day and record time plus time of last void on previous night OR collect 24 hour urine for 24, 48 and 72 hours after last exposure). Measure total volume and send aliquots to HEST for analysis.

Blood Collection: For all three groups, draw blood at 8 hours (or before second dose). On days 2-14 draw blood once a day just prior to one of the doses, as long as it is the same time for everyone. Draw blood once per day for 3 days of recovery after the 14th day.

Attachment 2. 14 -DAY HUMAN PERCHLORATE STUDY

Background: Sodium perchlorate, a treatment of hyperthyroidism, like the prophylaxis of iodine contamination zugelassenes medication, as a result of its properties to inhibit iodine uptake in the thyroid, and additionally to stimulate the excretion of iodine from the thyroid, is used clinically in the treatment of hyperthyroidism, however, predominently in the prevention of iodine contamination. For 60 years a series of side effects from sodium perchlorate have been reported. In the foreground of the altogether rare side effects is the development of a agranulocytosis. Fatal outcomes have been reported following application of higher doses and after longer use. In addition, there are side effects such as skin erruptions, gastrointestinal symptoms with nausea, toxic liver enzyme changes, as well as one case of renal syndrome published. Also in the absence of systematic evaluations of large series, retrospective studies of published observations are interpreted as sodium perchlorate dose-dependent. In a dose from 6 mg/kg/day there are no side effects reported according to our literature search. On the contrary, lacking, until now, are human studies of the effectiveness of a sodium perchlorate dose that is dose-dependent. In particular, the verification of earlier effects of smaller doses of medications for iodine supplementation for thyroid were hardly methodically tested in the past. The establishment of techniques for semiquantitative determination of gene expression from cytological aspirates will result in new possibilities for analysis. The molecular biological characterization of specific iodine transporters, of a sodium-iodine-symporter (NIS), moreover, allows a specific target gene for the control of thyroid iodine metabolism to be investigated. Analyses in *in vitro* systems show that NIS will be directly influenced by sodium perchlorate. Until now, no data exists about the control of NIS in humans under different condition of iodine supplementation. The planned study is directed at a characterization of NIS expression through sodium perchlorate in cytological aspirates of the thyroid gland. Through concurrent studies of thyroid function parameters in serum- and urine, iodine and sodium perchlorate levels data [generated] should be directed toward the lowering of given does of preparations in the prevention of iodine contamination. It will be expected that these studies and other studies will yield an important basis for the diagnostic application of semi-quantitative RT-PCR of NIS from aspirate materials from patients with thyroid disease in the different conditions of iodine supplementation. Early publications of iodine transporter show that NIS in [benign] nodules will be decreased and that possibly mutations in NIS of thyroid nodules underlies this. An establishment of this

technique can open possibilities to better answer the extraordinarily clinically relevant question of a better arrangement of nodule structures of the thyroid. According to epidemiological studies, up to 15% of the entire population of the Bundes Republik have thyroid nodules. Fortunately, fewer than 0.1% of these nodular structures undergo malignant transformation. A greater certainty in the differential diagnosis of thyroid nodules before this background would have been desirable.

Study Design:

Altogether, 7 volunteers after a 2-week placebo phase will be dosed with perchlorate for 2 weeks. The highest dose will be 12 mg/kg/day in a range that is customary for the prevention of iodine contamination in patients with thyroid disease and euthyroids (refs). Further dosings of 1 mg/kg/day as well as 0.1 mg/kg/day are planned. The maximum dose is comparable to a study [that we have done in] which we, while monitoring the modulation of TSH, T3, T4 with a total 3x300 mg of perchlorate over a time period of 3 weeks, have given to healthy volunteers. The results of this study are, as you gather by the accompanying publication [citation] was published a few years ago (ref). The Ethics Commission of the Hochschule had at that time agreed to our proposal (Proposal number 422) (18.10.1990 signed by Prof. Pichlmayr). The target parameter of control of thyroid function should [consist] of an ultrasonogram of the thyroid, a verification of thyroid hormone status with measurement of TSH, total T3, total T4, free thyroid hormone, thyroglobulin as well as the binding protein for thyroxin (TBG) at weekly intervals. Also, weekly assurance parameter such as blood picture, blood differential, liver enzymes SGPT [ALT], SGOT [AST], GGT, AP, LDH, and retention values of creatinine and uric acid will be determined. Further planned is to measure blood iodine as well as to obtain concentrations of urine creatinine (from spontaneous morning samples). The plasma level of sodium perchlorate should be measured directly in serum and in urine. A blood collection via a butterfly-canula is planned whereby within 30 minutes three blood samples (a total of 30 mls) will be taken, in order to control for possible time-dependent variations. In the 12 mg perchlorate/kg body weight group a collection after 30, 60, 90 minutes as well as after 2, 3, 4, 5, 6, 7 and 8 hours [einmalig] before the conclusion of therapy is planned (total of 100 ml whole blood). The target [decisions target/goal] of the study is the evaluation of the expression of sodium-iodine-symporters (NIS). In all dose groups [all participants will submit to] a thyroid aspiration at the [outset] as

well as at the end of the 4-week treatment; samples from which [will be used] in a RT-PCR amplification for NIS and structure genes for semiquantitative analysis of expression of iodine transporters. The technique of thyroid aspiration, a routine endocrinology procedure [has been practiced for more than 15 years by the proposal's director without complications].

Translation by:

William H. Baker, LTC, VC
Senior Pathologist
Operational Toxicology Branch
AFRL/HEST